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Industrialization, Electromagnetic Fields, and Breast Cancer Risk

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The disparity between the rates of breast cancer in industrialized and less-industrialized regions has led to many hypotheses, including the theory that exposure to light-at-night and/or electromagnetic fields (EMF) may suppress melatonin and that reduced melatonin may increase the risk of breast cancer. In this comprehensive review we consider strengths and weaknesses of more than 35 residential and occupational epidemiologic studies that investigated the association between EMF and breast cancer. Although most of the epidemiologic data do not provide strong support for an association between EMF and breast cancer, because of the limited statistical power as well as the possibility of misclassification and bias present in much of the existing data, it is not possible to rule out a relationship between EMF and breast cancer. We make several specific recommendations for future studies carefully designed to test the melatonin–breast cancer and EMF–breast cancer hypotheses. Future study designs should have sufficient statistical power to detect small to moderate associations; include comprehensive exposure assessments that estimate residential and occupational exposures, including shift work; focus on a relevant time period; control for known breast cancer risks; and pay careful attention to menopausal and estrogen receptor status. — *Environ Health Perspect* 107(Suppl 1):145–154 (1999). *http://ehpnet1.niehs.nih.gov/docs/1999/Suppl-1/145-154kheifets/abstract.html*

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Higher rates of breast cancer in industrialized compared to less-industrialized regions of the world have led to speculation regarding the possible etiologic roles of factors associated with increased economic development. Among the factors potentially associated with industrialization and breast cancer is the increased use of electric power and thus exposure to light-at-night and to electromagnetic fields (EMF). Over the past 2 decades, the association between EMF and cancer has been the subject of much controversy and scientific debate. Breast cancer is the only cancer for which there is a specific biologic mechanism proposed for the effect of EMF; thus, it is an area of particular interest. In 1987, Stevens (*1*) hypothesized that exposure to light-at-night and/or EMF may suppress melatonin and that reduced melatonin may increase the risk of breast cancer.

Melatonin is a hormone produced by the pineal gland. It has a marked circadian rhythm. Production of melatonin is low in the daylight hours and increases during the night. Exposure to light-at-night can suppress, delay, or interrupt the nightly synthesis of melatonin, which in turn may influence behavior, mood, hormone levels, or immune function. Most of the epidemiologic studies to date have used exposure to EMF as a proxy measure for increased exposure to light-at-night. Stevens' (*1*) hypothesis of the possible effects of melatonin suppression by EMF or light-at-night has provided a useful framework for considering how EMF could affect breast cancer risk. According to Stevens (*1*), EMF or light-at-night and its effect on melatonin may affect the risk for breast cancer in three ways. First, if melatonin suppresses reproductive hormones such as estrogen, melatonin suppression could allow estrogen levels to rise, stimulating growth in breast tissue and estrogen-responsive breast cancers. Second, if melatonin suppresses breast cancer cell growth directly, reduction in melatonin could allow breast cancers to grow more rapidly. Third, if melatonin boosts immune function, melatonin suppression could compromise the immune system's ability to control cell transformation.

This paper reviews the epidemiologic literature that has investigated the association between EMF and breast cancer. Studies investigating the risk of breast cancer associated with residential EMF exposure, electric blanket use, and occupational exposure to EMF are included. Only English-language studies published in scientific peer reviewed journals are included in this review. Studies were identified through extensive literature searches and suggestions from experts in the field.

Epidemiology of Breast Cancer

Breast cancer is the most commonly occurring malignancy in American women, representing approximately 32% of all female cancers in the United States (*2,3*). Among cancers, the mortality rate for female breast cancer is second only to that of lung cancer. In the United States in 1995 there were an estimated 182,000 new cases and 46,000 deaths due to breast cancer (*2*). It is expected that 1 of 8 females will develop breast cancer in her lifetime (*2,4*). The incidence of breast cancer increased in the 1980s, especially from 1980 to 1987 but has since leveled off (Figure 1) (*5,6*). Incidence rates are highest among white women for postmenopausal breast cancer and highest among black women for premenopausal cancer. Mortality from breast cancer has been steady over the past 2 decades with similar rates for whites and blacks, though recently mortality among blacks has been slightly higher than mortality among whites (*2,7*). Breast cancer rates are highest in North America and northern Europe and lowest in Asia and Africa, though there is evidence that rates are increasing in several Asian and central European countries (*2,8,9*). Male breast cancer is rare, occurring in approximately 900 men each year in the United States (*2*).

There are several established risk factors for breast cancer in females (*2,5,8,10–13*). The disease increases with age and is found most commonly among women of upper social class, women without children or with few children, and women who have their first child at an older age. Other risk factors include early age of menarche, late age at menopause, thinness among premenopausal women, obesity among postmenopausal women, proliferative fibrocystic disease, and a first-degree relative with breast cancer, especially if diagnosed at a young age. Recently identified mutations in

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Abbreviations used: CI, confidence interval; EMF, electromagnetic field(s); HCC, high-current electric wiring configuration; OR, odds ratio; PIR, proportional incidence ratio; RR, relative risk; SES, socioeconomic status; SIR, standard incidence ratio; SMR, standard mortality ratio.

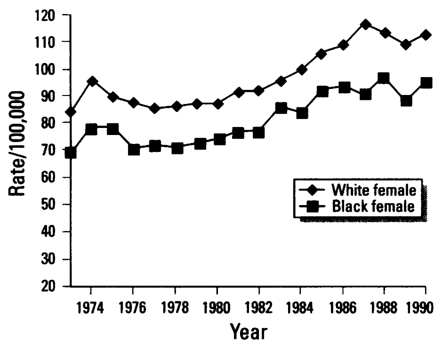

Figure 1. Female breast cancer incidence (*5*).

the *BRCA1* and *BRCA2* genes associated with breast cancer at an early age have increased our understanding of the genetic component of this disease but are likely to account for only a small percentage of cases (*2*). Although there are many established risk factors, there is still much uncertainty surrounding other risk factors such as the use of estrogen therapy and oral contraceptives, alcohol consumption, and physical activity level.

Reasons for the international variation in incidence and mortality of breast cancer remain uncertain, with industrialization proposed as a possible explanation. Industrialization, however, brings many changes and it is unclear what aspects of industrialization are the most relevant in terms of breast cancer epidemiology. Studies of immigrants to the United States indicate that environmental factors are mainly responsible for the international variation in rates (*2,8,14,15*). Several reproductive characteristics change with urbanization and are likely to be responsible for at least some of the above-mentioned differences in rates (*16*). In addition, many other risk factors that relate to the degree of urbanization must be considered potential explanations for the international variation in rates. These factors include breast-feeding, long-term use of oral contraceptives, use of estrogen replacement therapy, use of diethylstilbestrol during pregnancy, alcohol consumption, and physical activity level. Finally, environmental and occupational exposure to chemicals such as organochlorines and related pesticides, polycyclic aromatic hydrocarbons including those from cigarette smoking, and other exposures have been suggested as potential causes (*17–19*). Presently, little is known definitively about environmentally induced breast cancer, about reasons for the observed worldwide increases in breast cancer incidence, or about reasons for the international variation in rates.

Even less is known about the risk factors for male breast cancer, although it is thought that there are both environmental and genetic components including obesity, family history, and endocrine factors (*3,20*).

Residential Studies

Proximity to Power Lines

Several studies have investigated the effect of residential EMF exposure, usually defined in terms of proximity to power lines, and the risk of adult cancers, including breast cancer. Of the studies that have addressed the risk of breast cancer and residential exposure to EMF, only the first study (*21,22*) showed an effect (Table 1).

Wertheimer and Leeper (*21,22*) found an association between high-current electric wiring configuration (HCC) and breast cancer in a case–control study conducted in Colorado. The study compared residence in HCC homes among 1179 cases of adult cancers with the residences of matched controls. In this death-certificate-based study, controls were selected from noncancer deaths and matched to the cancer case for town, age, sex, year of death, year when the subject lived in the house, and socioeconomic level of the census tract. There was an overall increase in breast cancer risk among those living in HCC residences (odds ratio [OR] = 1.6, $p < 0.01$); however, this effect was attributed to an effect among premenopausal women (OR = 2.87, no confidence interval [CI] available) with no

Table 1. Residential proximity to electrical installations and risk of female breast cancer.

Reference, year	Study location, country	Study design	Sample size	Exposure	Results
Wertheimer and Leeper,[a] 1982 (*21*) and 1987 (*22*)	U.S. (Colorado)	Case–control, death certificates	140 matched pairs of breast cancer discordant on exposure	HCC vs LCC	OR = 1.64 ($p \leq 0.01$) premenopausal women
McDowall,[a] 1986 (*23*)	England	Cohort	3861—22 cases	Living ≤ 50 m from electrical installation equipment or ≤ 30 m from an overhead power cable	SMR = 1.06 (0.66–1.60)
Schreiber et al.,[a] 1993 (*24*)	Netherlands	Cohort	1774—14 cases	Living ≤ 100 m from electrical transmission equipment	SMR = 0.96 (0.31–2.23)
Verkasalo et al.,[a] 1996 (*25*)	Finland	Cohort	194,400—1229 cases	Living ≤ 500 m from overhead transmission lines with calculated magnetic field exposure > 0.01 µT	RR = 0.95 (0.88–1.02)
Li et al., 1997 (*26*)	Taiwan	Case–control	1980 cases, 1880 controls	Distance from transmission line, > 100 m used as reference	< 50 m: OR = 1.0 (0.9–1.3) 50–99 m: OR = 1.2 (0.9–1.5)
Feychting et al., 1998 (*27*)	Sweden	Case–control	699 cases, 699 controls	Living within 300 m of 220 or 400 kV power lines with calculated magnetic field exposure > 0.1 µT	Exposure level = 0.1–0.19 µT All women: OR = 1.2 (0.8–1.8) Women < 50: OR = 1.2 (0.6–2.8) Women ≥ 50: OR = 01.2 (0.7–1.9)
Feychting et al., 1998 (*27*)	Sweden	Case–control	699 cases, 699 controls		Exposure level = ≥ 0.2 µT All women: OR = 1.0 (0.7–1.5) Women < 50: OR = 1.8 (0.7–4.3) Women ≥ 50: OR = 0.9 (0.5–1.4)

Abbreviations: HCC, high-current electric wiring configuration; LCC, low-current electric wiring configuration. [a]Although these studies included men, there were not enough data to assess risk among males.

effect among postmenopausal women (OR = 1.16, no CI available). Breast cancer was considered premenopausal if diagnosed prior to age 55 and postmenopausal if diagnosed after age 55. This type of classification based only on age at diagnosis inevitably leads to some misclassification of menopausal status.

McDowall (*23*) followed approximately 8000 people (3861 women) from 1971 through 1983 who were living within a 50-m radius of electrical transmission facilities at the time of the 1971 census in East Anglia, England. Among this cohort the overall mortality was lower than expected and there was no evidence of increased risk for breast cancer (standardized mortality ratio [SMR] = 1.1, CI = 0.7–1.6). In another study, Schreiber et al. (*24*) identified 3549 people (1774 women) who lived for at least 5 years from 1956 to 1981 in an urban quarter of the Netherlands. The area had two 150-kV power lines and one transformer substation. There was no increased risk of breast cancer among those living within 100 m of the installations (SMR = 1.0, CI = 0.3–2.2); paradoxically, those living > 100 m from the installations had higher risk (SMR = 1.3, CI = 0.6–2.4), although the confidence intervals were wide and overlapping.

Verkasalo et al. (*25*) studied a cohort of 383,700 Finnish people, including 194,400 women who lived within 500 m of overhead transmission lines in homes with calculated magnetic fields > 0.01 µT (0.1 mG) during 1970 to 1989. Data on the location, voltage, apparent power, and tower types of the 110 to 400 kV lines were provided by Finnish power companies. Power line routes were then linked to the Finnish registry of buildings and residences as well as the Finnish central population register. There was no significant association or dose–response relationship observed with residential proximity to power lines and incidence of breast cancer (relative risk [RR] = 1.0, CI = 0.9–1.0).

Recently, Li et al. (*26*) reported results from a case–control study of residential exposure to magnetic fields and adult cancer in Taiwan. Women with newly diagnosed breast cancer from 1987 to 1992 were matched to controls with other types of cancer (excluding cancers thought to be related to EMF) based on date of birth and date of diagnosis. Exposure was defined in terms of distance from transmission lines as well as estimated residential magnetic field exposure in the year of diagnosis. There was no association between breast cancer and living less than 50 m from transmission lines (OR = 1.0, CI = 0.8–1.3), nor was there an increased risk among the highest exposure group, > 0.2 µT (OR = 1.1, CI = 0.9–1.3).

In a population-based case–control study from Sweden, Feychting et al. (*27*) also investigated the effects of exposure to EMF and risk of breast cancer. Women living in a single-family residence within 300 m of a 220- or 400-kV power line for at least 1 year between 1960 and 1985 were eligible for the study. Cases were identified through linkage with the Swedish National Cancer Registry. A total of 699 female cases and 699 age-matched controls were included in the analysis. Feychting et al. (*27*) observed no overall increase in the risk of female breast cancer associated with increased estimate of EMF exposure. This result did not change when adjusted for socioeconomic status (SES). Although there was an increased risk associated with the highest exposure group for women younger than 50 years of age (OR = 1.8, 95% CI = 0.7–4.3), the number of cases was small ($n = 15$) and the CI was wide. This result was more pronounced for estrogen-receptor-positive cases, but again, the numbers were limited.

Because breast cancer is rare in males, there were not enough data in these studies to examine an association in males. Even for females most studies did not have enough power to detect a small to moderate association (*28*). Feychting et al. (*27*) reported an elevation in risk with residential exposure, but the results were not significant and were based on only nine cases of male breast cancer (OR = 2.1, 95% CI = 0.3–14.1).

Electric Blanket Use

The use of electric blankets has been examined as a risk factor for breast cancer because of the potential for prolonged exposure to increased EMF. There has been limited investigation of the use of electric blankets and the risk of breast cancer in women. In 1991 Vena et al. (*29*) published data from a case–control study of electric blanket exposure among 382 cases of breast cancer and 439 randomly selected community controls in New York State from 1987 to 1989. This study was limited to postmenopausal women and results were adjusted for age and education. Histories of electric blanket use were obtained through interviews at home. Electric blanket exposure was defined as any use in the past 10 years, frequency of use by seasons, and use through the night. There was no significant association with any level of exposure and no dose–response effect.

In a second study published in 1994, Vena et al. (*30*) did a similar study of electric blanket use, this time among premenopausal women. The western New York study included 290 premenopausal cases of breast cancer and 289 age-matched randomly selected community controls from 1986 to 1991. Again the authors concluded that there was no evidence to support the hypothesis that the use of electric blankets increases the risk of breast cancer.

Following a suggestion by Stevens (*31*), the authors combined the data from the premenopausal and postmenopausal women and reanalyzed the data (*32*) (Table 2). Although there was a significantly increased risk of breast cancer associated with some use of an electric blanket through the night in the previous 10 years (OR = 1.5, CI = 1.1–1.9), there was no evidence of a dose–response effect. In fact the OR was not as elevated and the confidence interval included the null value in the highest exposure category; that is, for those who used the blankets in the cool seasons and continuously through the night for 10 years the OR = 1.2 with CI = 0.8–1.9.

In a larger, more recent, population based case–control study, Gammon et al. (*33*) reported that ever using electric blankets, mattress pads, or heated water beds did not increase the risk of breast cancer among premenopausal (OR = 1.0, CI = 0.8–1.2) or postmenopausal women (OR = 1.1, CI = 0.8–1.5). This study included 2202 women younger than 55 years of age with incident cases of breast cancer between 1990 and 1993 in three geographic regions of the United States (Atlanta, Georgia; New Jersey; and Washington State). There were 2009 controls that were frequency matched to cases by 5-year age group and geographic area. However, the New Jersey and Washington State study sites included only women younger than 45 years of age. The data for postmenopausal women are based on the women in Atlanta only, which included women up to 55 years of age. Although EMF exposure was not a primary focus of this study, all women were asked about their use of electric blankets. Gammon et al. (*33*) concluded that the data did not support the hypothesis that electric blanket use increases breast cancer risk among pre- or postmenopausal women.

Table 2. Electric blanket use and risk of breast cancer in women.

Reference, year	Subjects	Cases/ controls, *n*	Ever use[a] OR	Ever use[a] 95% CI	Daily use OR	Daily use 95% CI	Use through the night[b] OR	Use through the night[b] 95% CI	Long-term use[c] OR	Long-term use[c] 95% CI
Vena et al., 1991 (*29*)	Postmenopausal	382/439	0.89	0.66–1.19	0.97	0.70–1.35	1.31	0.88–1.95	1.25	0.73–2.16
Vena et al., 1994 (*30*)	Premenopausal	290/289	1.18	0.83–1.88	1.27	0.86–1.88	1.10	0.59-2.05	1.43	0.94–2.17
Vena et al. (*29,30*), combined results	Postmenopausal and premenopausal	672/728	1.07	0.9–1.4	1.16	0.90–1.50	1.45	1.08–1.94	1.23	0.81–1.87
Gammon et al.,[d] 1998 (*33*)	Premenopausal and postmenopausal[e]	1647/1498 526/489	0.98 1.05	0.83–1.16 0.79–1.39	N/A N/A	N/A N/A	1.01 1.08	0.85–1.20 0.80–1.45	0.88 0.89	0.75–1.04 0.63–1.25

[a]Defined as any use during the last 10 years for Vena et al. (*29,30*) and as ever use for Gammon et al. (*33*). [b]Defined as use through the night for Vena et al. (*29,30*) and as on most of the time for Gammon et al. (*33*). [c]Defined as use through the night in-season for 10 years for Vena et al. (*29,30*) and as longer than 24 months for women < 45 years of age and longer than 22.5 months for women ≥ 45 years of age for Gammon et al. (*33*). [d]Women < 45 years of age includes women from New Jersey, Washington, and Atlanta, GA; women ≥ 45 years include women from Atlanta only. [e]Premenopausal women defined as those < 45 years of age; postmenopausal women defined as those > 45 years of age.

There have been no studies on the use of electric blankets and male breast cancer.

Occupational Studies

Female Breast Cancer

Few occupational studies of electrical workers include sufficient numbers of females to address the potential association of occupational EMF exposure and the development of breast cancer. Several of the cohort studies that have investigated the association between female breast cancer and electrical occupations have shown no effect (*34–36*) (Table 3). Two of the studies were large cohorts based in England and Denmark with limited exposure assessment (exposure was based on job titles alone) (*35,36*). Furthermore, the study from England was not a population-based study; the cohort was derived from a cancer registry and included only those with valid occupational data (36% of the entire registry cohort from 1981–1987) (*36*). Although a study based in Sweden had better exposure measurement (work histories), it was limited by sample size (only seven cases of breast cancer) (*34*). However, a cohort study from Norway based on 50 cases (*37*), with exposure based on a combination of job titles and some measurements, reported an increased risk of breast cancer among radio and telegraph operators (standardized incidence ratio [SIR] = 1.5, CI = 1.1–2.0).

Of the case–control studies that have investigated the risk of breast cancer among women in electrical occupations, the results have varied, particularly by menopausal status (*36–40*). One of the largest occupational studies of EMF and breast cancer among women was reported by Loomis et al. (*38*) in 1994. They conducted a case–control study using computerized mortality files from the National Center for Health Statistics for the years 1985 to 1989. Occupation and industry information from death certificates was coded according to the 1980 U.S. census. Women whose occupations were listed as homemakers or whose death certificates provided no occupational data were excluded. These exclusions made up more than half the database. Seven electrical occupations used in previous studies were included along with seven other occupations, such as computer programmers and telephone operators, presumed to have a large number of female workers and some potential for above-background EMF exposure. All other occupations were considered unexposed.

Among 27,882 women who died of breast cancer and 110,949 controls (women who died of any other cause, excluding brain cancer and leukemia), 68 cases and 199 controls had been employed in traditional electrical occupations. The relative risk for breast cancer among those classified as employed in electrical occupations was 1.38 (CI = 1.0–1.8). In a more detailed analysis, a statistically significant increased risk was demonstrated among electrical workers 45 to 54 years of age (OR = 2.2, CI = 1.2–4.0) but not in younger or older women. No risk was seen for other occupations with potential for exposure (OR = 0.8, CI = 0.4–1.3). In a separate analysis of the same dataset, Cantor et al. (*39*) did not find an association between potential workplace exposure to EMF and breast cancer. The study by Cantor et al. extended the time period under investigation and regrouped exposure, including occupational exposure to extremely low frequency fields.

In a large population-based case–control study, Coogan et al. (*40,41*) investigated the association between occupations with potential for exposure to 60-Hz magnetic fields and the incidence of female breast cancer. Female residents of Maine, Wisconsin, Massachusetts, and New Hampshire who were 74 years of age or younger and who were reported to the state cancer registries with newly diagnosed cases of breast cancer between 1988 and 1991 were eligible for the study. Controls were randomly selected from driver's license and Medicare lists. Occupational information and information on reproductive history and other breast cancer risk factors were obtained by telephone interview. Usual occupation and industry were coded according to the 1980 U.S. census codes. Potential for exposure to 60-Hz magnetic fields was coded as high, medium, low, or background level. Among a total of 6888 cases and 9529 controls, Coogan et al. (*40,41*) reported a somewhat higher risk for the highest exposed premenopausal women (OR = 2.0, CI = 1.0–3.8) than for similarly exposed postmenopausal workers (OR = 1.3, CI = 0.8–2.2). The overall risk in the high-exposure category was 1.43 (CI = 1.0–2.1).

In a nested case–control analysis of radio and telegraph workers from Norway, Tynes et al. (*37*) investigated the effect of shift work as a surrogate for light-at-night exposure. They observed no effect of shift work in women younger than 50 years of age but did report a significant increase in risk among the highest

Table 3. Occupational exposure to electromagnetic fields and risk of breast cancer in females.

Reference, year	Country	Study design	Sample size	Exposure	Exposure assessment	Results
Vågerö et al., 1985 (*34*)	Sweden, 7 cases	Cohort	867 (7 cases)	Telecommunication industry workers	Work history	SMR = 0.6 (0.3–1.3)
Guénel et al., 1993 (*35*)	Denmark	Cohort	1,402,223: (1526 cases intermittent exposure), (55 cases continuous exposure)	Occupations with potential EMF exposure; intermittent or continuous	Job title	Intermittent exposure, Obs/exp = 0.96 (0.91–1.01) Continuous exposure, Obs/exp = 0.88 (0.68–1.15)
Loomis et al., 1994 (*38*)	U.S.	Case–control[a]	28,434 cases, 113,011 controls	Electrical workers	Job title, n = 68 cases exposed	OR = 1.38 (1.04–1.82)
Cantor et al., 1995 (*39*)	U.S.	Case–control[a]	Whites 29,397 cases; 102,955 controls Blacks 4112 cases; 14,830 controls	Electrical workers	Job title, exposure matrix	Exposure level Whites Med: OR = 1.10 (1.03–1.2), High: OR = 0.97 (0.8–1.2) Blacks Med: OR = 1.29 (1.1–1.5), High: OR = 1.19 (0.7–2.1)
Coogan et al., 1996 (*40*)	U.S.	Case–control	6888 cases, 9529 controls	Potential for exposure to 60-Hz magnetic fields	Usual occupation from interview, exposure classification by hygienist	Exposure level Low: OR = 1.02 (0.91–1.15), Med: OR = 1.09 (0.83–1.42), High: OR = 1.43 (0.99–2.09)
Fear et al., 1996 (*36*)	England	PIR	252,663 men, 14 cases; 119,227 women, 83 cases	Electrical workers	Job titles	PIR For men = 1.3 (0.7–2.2) For women = 0.9 (0.7–1.1)
Tynes et al., 1996 (*37*)	Norway	Cohort	2619 (50 cases)	Radio and telegraph operators	Job titles, some measurements	SIR = 1.5 (1.1–2.0)
Tynes et al., 1996 (*37*)		Nested case–control	50 cases, 259 controls	Potential exposure to light-at-night (shift work)	Job titles, some measurements	Exposure level Women < 50 years of age Low: OR = 0.3 (0.1–1.2), High: OR = 0.9 (0.3–2.9) Women ≥ 50 years of age Low: OR = 3.2 (0.6–17.3), High: OR = 4.3 (0.7–26.0)
Kelsh and Sahl 1997 (*61*)	U.S.	Cohort	9788 (26 cases)	Electric utility workers	Usual occupation	SMR = 0.80 (0.52–1.17)

Abbreviations: obs/exp, observed/expected number of cases; PIR, proportional incidence ratio. [a]Case–control analysis of death certificate data.

exposed postmenopausal women (defined as older than 50 years of age [OR = 4.3, CI = 0.7–26.0]).

Of all the studies of EMF exposure and female breast cancer, case–control studies of occupational exposure are the most suggestive. Although it could be argued that cohort studies conducted to date did not have sufficient power, case–control studies have problems of their own: the most severe problem is the lack of even rudimentary exposure assessment. Other methodologic issues include the use of death certificate data and the lack of information on potential confounders.

Male Breast Cancer

Table 4 shows the results from both cohort and case-control studies of EMF and male breast cancer (*35,36,42–51*). Several of the large occupational studies of EMF and adult cancer in males could not be included because there were insufficient details and too few cases (*52–61*). Most of the cohort studies show no effect of electrical occupations on the risk for male breast cancer. However, in a study in Norway in 1992, Tynes et al. (*46*) reported an increased risk among electrical workers (SIR = 2.1, CI = 1.1–3.6). Floderus et al. (*47*) reported an increased risk among Swedish railway workers in 1961 to 1969 (OR = 4.3, CI = 1.6–11.8) but not in the 1970 to 1979 time period.

Like the cohort studies, most of the case–control studies among men show no effect of electrical occupations on risk for breast cancer. However, in a large study from the United States, Demers et al. (*48*) reported an increased risk of breast cancer among workers in occupations with potential EMF exposure (OR = 1.9, CI = 1.0–3.7). In the large, more recent, well-conducted studies of electrical workers (*61,49,50*), there was no excess of male breast cancer. However, even in large occupational studies using thousands of workers, it is difficult to ascertain sufficient cases of breast cancer among men to investigate the relationship between EMF and male breast cancer.

Dose–Response Relationships

Most of the studies of EMF and breast cancer have categorized EMF exposure into a reference group and one level of exposure. Thus, there are few data on the possible dose–response effect of EMF on breast cancer risk. In the two most recent studies of residential proximity to power lines, both Li et al. (*26*) and Feychting et al. (*27*) report higher relative risks among those with the highest exposure levels. However, in both cases the confidence intervals are wide and overlapping and include the null value. There appeared to be no clear dose–response effect in the studies of electric blanket use. Five of the occupational studies provided data on at least two levels of potential EMF exposure (Figure 2) (*37,39,41,48,51*). Only two of

Table 4. Occupational exposure to electromagnetic fields and risk of breast cancer in males.

Reference, year	Country	Study design	Sample size	Exposure	Exposure assessment	Result
Matanoski et al., 1991 (*42*)	U.S.	Cohort	50,582, 2 cases	Telephone workers	Current job title, some measurements	SIR = 6.5 (0.79–23.5)
Demers et al., 1991 (*48*)	U.S.	Case–control	227 cases, 300 controls	Occupations with potential EMF exposure	Work history, n = 33 cases exposed	All exposed jobs OR = 1.85 (1.0–3.7)
Tynes et al., 1992 (*46*)	Norway	Cohort	37,945; 12 cases	Electrical workers	Job title; estimated type of exposure	SIR = 2.07 (1.07–3.61)
Loomis, 1992 (*43*)	U.S.	Case–control	250 cases, 2500 controls	Electrical occupations	Job title, n = 4 cases exposed	OR = 0.9 (0.34–2.40)
Guénel et al., 1993 (*35*)	Denmark	Cohort	154,000: intermittent exposure (23 cases) 18,000: continuous exposure (2 cases)	Occupations with potential EMF exposure; intermittent or continuous	Job title	Intermittent exposure Obs/exp = 1.22 (0.77–1.83) Continuous exposure Obs/exp = 1.36 (0.16–4.91)
Floderus et al., 1994 (*47*)	Sweden	Cohort	1961–1969 17,150,940 person-years 1970–1979: 19,056,600 person-years	Railway workers	Job title	1961–1969 Railway workers, 4 cases; RR = 4.3 (1.6–11.8); Railway industry, 4 cases; RR = 2.1 (0.8–5.8) 1970–1979 Railway workers, 0 cases; Railway industry, 4 cases; RR = 0.9 (0.3–2.5)
Thériault et al., 1994 (*49*)	Canada, France	Case–control	Electricite de France—Gaz de France: 170,000, 3 cases; Ontario Hydro: 31,543, 3 cases; Hydro-Quebec: 21,749, 1 case	Electric utility workers	Work history, some measurements	7 cases observed, 8.5 expected (numbers too small for formal analysis)
Tynes et al., 1994 (*44*)	Norway	Cohort	5088, 1 case	Hydroelectric power company workers	Work history, exposure estimates (no measurements)	SIR = 1.4 (0.03–7.6)
Rosenbaum et al., 1994 (*45*)	U.S.	Case–control	71 cases, 256 controls	Occupational exposure to EMF	Job title, n = 6 cases exposed	OR = 0.6 (0.2–1.6)
Savitz and Loomis, 1995 (*50*)	U.S.	Cohort	138,905, 6 cases	Electric utility workers	Work history, some measurements	SMR = 0.80 (0.29–1.74)
Fear et al., 1996 (*36*)	England	PIR	252,663 men, 14 cases 119,227 women, 83 cases	Electrical workers	Job titles	PIR For men = 1.3 (0.7–2.2) For women = 0.9 (0.7–1.1)
Stenlund and Floderus 1997 (*51*)	Sweden	Case–control	56 cases, 1121 controls	Occupational exposure to EMF	Work history, job exposure matrix, some measurements	OR = 0.7 (0.3–1.9)

these studies had estimates of EMF levels based on any measurements—one showing a higher risk for higher exposure (*37*) and one showing no difference in risk (*51*). Evidence for a dose–response effect of EMF and risk of breast cancer is not consistent. Comparison of the potential for a dose–response effect of EMF across such a limited number of studies, all of which were deficient in exposure assessment and had different exposure groupings, should be done with caution. Misclassification is further exacerbated by the fact that the relevant time period of exposure is unknown and many of the exposures occurred in the distant past.

Effects of Menopausal Status

Because several risk factors for breast cancer differ by menopausal status, it is important to examine whether the effect of EMF on breast cancer risk varies by menopausal status. On the basis of Stevens' (*1*) hypothesis, we would expect that if estrogen were involved in the pathway between EMF, melatonin, and breast cancer, the relationship between breast cancer risk and EMF would vary by menopausal status. Because melatonin may affect the release of estrogen by the gonads, premenopausal women may be more likely

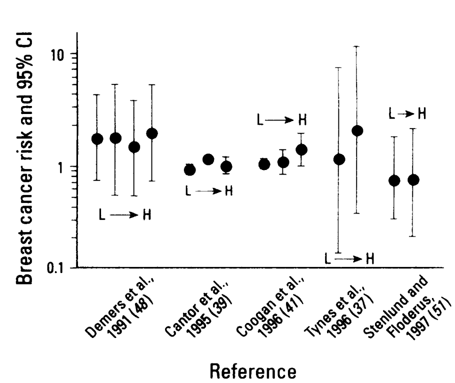

Figure 2. Level of exposure and risk of breast cancer in women. Abbreviations: H, high; L, low.

to be influenced by exposure to EMF compared to postmenopausal women. Alternatively, if melatonin acts on circulating estrogen levels, its affect may be more important to postmenopausal women whose endogenous levels of estrogen are low compared to those of premenopausal women. For example, obesity is a risk factor for postmenopausal breast cancer because it is thought that the conversion of estrogen in adipose tissue is more important to the postmenopausal woman whose endogenous estrogen levels are low (*2*). Finally, a direct effect of melatonin suppression on breast cancer growth or a generalized immune effect would not necessarily suggest a difference in risk between pre- and postmenopausal breast cancers associated with EMF or light-at-night.

Although most studies did not separate pre- and postmenopausal breast cancers, five studies considered the effect of menopausal status. In most of these studies the pre- or perimenopausal women were at somewhat higher risk for breast cancer as compared to postmenopausal women (Figure 3). The Tynes et al. (*37*) study was the only study to conclude that postmenopausal women were at increased risk for breast cancer compared to premenopausal women. It is important to note that the Tynes et al. (*37*) study based the menopausal status on age alone and was the only study of shift work, which might be a better proxy for light-at-night than EMF.

Discussion

Evidence from epidemiologic studies on EMF and breast cancer is inconsistent. Most of these studies were not designed to

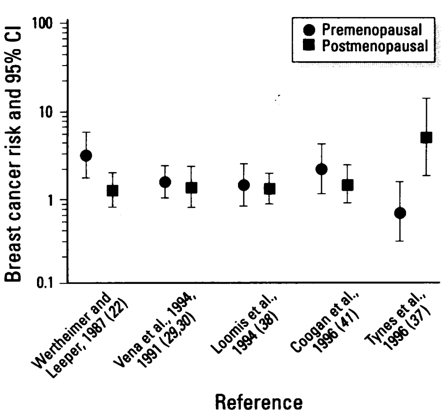

Figure 3. Comparison of pre- and postmenopausal breast cancer risk and residential or occupational EMF exposure. The Loomis et al. (*38*) study showed the highest perimenopausal OR [OR = 2.2 (1.2–4.0)].

specifically address this hypothesis and thus provide a limited test of it. Small numbers, rudimentary exposure assessment, and lack of information on other factors are among the most important limitations of studies to date. In addition there are other potential explanations for the differences in breast cancer rates between industrialized and nonindustrialized regions including differences in diet, alcohol consumption, contraceptive use, physical activity patterns, reproductive behaviors, and exposures to chemicals.

In the studies of residential proximity to power lines, there is little evidence to support an association between EMF and female breast cancer risk. Among the few residential exposure studies that have been done, the definition of exposure to high residential EMF exposure has varied from those living within 50 to 500 m of transmission lines to those who live in homes near HCC. It is not possible to determine whether the discrepant results between the studies were due to chance or whether better exposure measurement would make a real effect of EMF (or lack of an effect) more apparent.

The ability to detect an association between wire codes and breast cancer could be influenced by the confounding effect of some other factor associated with distance from the power lines and breast cancer. Common correlates of urbanization and wire codes include traffic density and SES. There is no known association between traffic density and breast cancer; thus it is not considered a potential confounder. On the other hand, SES has been associated with both increased distance from power lines and increased risk of breast cancer. However, all of the studies that investigated the association between residential proximity to power lines and breast cancer controlled for SES (*21,23,26–27*), with the exception of the study by Schreiber et al. (*24*). Interestingly, the Schreiber et al. (*24*) study reported a higher association between increased distance from the power lines and breast cancer.

In the limited studies of the effect of electric blanket use and female breast cancer, the evidence does not support an effect of EMF on breast cancer risk and does not provide evidence of a dose–response relationship. However, investigators initially thought that the use of electric blankets would lead to higher exposures than actually exist. Careful studies of electric blankets and pregnancy outcomes that included measurements demonstrated that exposures to EMF from electric blankets were not as high as previously thought (*62,63*). Thus studies that categorize exposure based solely on questions regarding blanket use are subject to large and potentially differential misclassification.

No study thus far has considered the effect of all possible residential exposures to EMF—including exposure to appliances, electric blankets, and power lines—and occupational exposures on the risk for breast cancer.

Among the occupational studies, the data are limited for women because of the relatively few women in electrical occupations on which these studies are focused. These limited data do not support the association between EMF and female breast cancer. The exceptions are the Loomis et al. (*38*) study, which showed an effect overall and in peri-menopausal women, and the Coogan et al. (*41*) study, which showed an effect in the highest exposed premenopausal women but not postmenopausal women. Both studies have methodological shortcomings, most importantly exposure assessment.

Among males, most studies have not had sufficient power to detect an association with EMF or electrical occupations because male breast cancer is so rare. Although some studies have shown a positive association between EMF and breast cancer, the data are not consistent and the magnitude of the effect, if any, does not appear large.

In addition, among the few studies with data on multiple levels of exposure, there is no clear pattern of a dose–response relationship between higher EMF exposure and increased risk for breast cancer. However, the definitions of exposure have not been uniformly careful or consistent, which makes it difficult to detect a dose response or to compare studies.

Occupational studies of EMF and breast cancer face particular challenges of exposure assessment. The validity of the studies depends on the accuracy of the occupational information, often reported on death certificates or population registries, and to the extent that job titles alone reflect exposure to magnetic fields. Also, control for potential confounders such as reproductive factors and family history of breast cancer are not usually possible in large-scale occupational studies. It is unknown whether women working in male-dominated fields are more likely to be nulliparous, be older at first childbirth, or have other characteristics associated with breast cancer. Lack of control for confounders may have biased studies toward or away from the null value, whereas large exposure misclassification is more likely to produce bias to the null.

The ability to more carefully define the relevant exposure of interest seems to be a crucial challenge for future studies. One of the unknown factors is the timing of exposure. For example, long-standing controversy over oral contraceptive use and breast cancer appears to be resolved by a recent reanalysis of several studies that found that only the current oral contraceptive users were at an increased risk (*64*). Future studies should be designed with an ability to better capture recent and past exposures.

The crux of Stevens' (*1*) hypothesis is that exposure to light-at-night or EMF disrupts the body's natural circadian rhythm of melatonin production. Interestingly, only one study (*19*) looked at shift work as an exposure to light-at-night, and this is the only study that showed an increased risk for postmenopausal women.

Understanding the implications of menopausal status and estrogen is also important in elucidating the potential relationship between EMF and breast cancer. More careful definitions of menopause, not just using age as a marker of menopausal status, seems crucial if the relationship between EMF, menopause, and estrogen is to be understood. Most studies have used age as a proxy of menopausal status, which leads to misclassification and bias. Determining whether the breast cancer cases are estrogen-receptor positive may also help in defining the possible role of melatonin. In addition, progesterone receptor status may also be informative.

Some evidence to support the Stevens (*1*) hypothesis of an EMF, melatonin, and breast cancer link has come from animal, laboratory, and human studies (*65*). In virtually all mammals, including humans, exposing the eyes to bright light at night can suppress, delay, or interrupt the nightly synthesis of melatonin. Studies of the effects of EMF on melatonin are not consistent (*66*). In whole-animal experiments on rodents with tumors, the vast majority of experiments report that deprivation of pineal function, either surgically or functionally, enhances tumor incidence, multiplicity, or size, or reduces tumor latency. Furthermore, melatonin treatments either partially counteract pinealectomy or are, by themselves, beneficial in animals with intact pineal function and normal photoperiod. Melatonin treatment does not in any simplistic way restore what pinealectomy removes. Thus, the oncostatic activity of the pineal gland and melatonin is likely to be physiologically complex.

The majority of *in vitro* studies on human breast tumor MCF-7 cells cultured in monolayer consistently demonstrate optimal antiproliferative effects at a physiologic concentration of melatonin. In contrast, pharmacologic doses of melatonin are needed to produce maximal effects in MCF-7 cultures that are not in an anchored monolayer culture, and in other lines of estrogen-receptor-positive human breast tumor cells cultured as monolayers. There is a suggestion, however, that there may be nonmelatonin substances from the pineal gland that are immunostimulatory.

The majority of studies report that EMF exposure suppresses melatonin in small animal species. Despite the abundant data showing that EMF exposure is associated with melatonin suppression in these animals, there have been difficulties in reproducing some of the results both between different laboratories as well as within single laboratories. In addition, studies with sheep, baboons, and humans mostly show no effect of EMF exposure on circulating melatonin or urinary aMT6-s.

There is some evidence that melatonin suppresses mammary tumorigenesis (*67,68*). Other studies have shown that melatonin can inhibit estrogen-induced proliferation of human breast cancer cells *in vitro* (*69*). Similarly, early human laboratory studies showed magnetic field melatonin suppression among individuals with low melatonin levels (*66*). These findings were not confirmed in a similar study with a stronger experimental design. Kaune et al. (*70*) investigated whether exposure to magnetic fields and/or light-at-night is associated with melatonin suppression. Relatively small suppression (10%) by magnetic fields was seen among women using medications that might suppress melatonin. Given the large natural variability in melatonin levels among individuals (≥ 5-fold), the health consequences of small melatonin reductions are unclear. Nevertheless, this finding needs to be replicated because it represents an important step in Stevens' (*1*) hypothesis. Finally, in a study by Hahn (*71*), women who had profound bilateral blindness, and were thus not sensitive to the effects of light-at-night on melatonin levels, were at decreased risk for breast cancer compared to sighted women. Thus, although evidence is accumulating to support the potential role of melatonin in carcinogenesis, questions remain regarding the ability of EMF to suppress melatonin. Studies of breast cancer occurrence in individuals with naturally low and high melatonin levels would provide a crucial piece to this puzzle and are urgently needed.

The use of the traditional large databases of electrical workers, which is common among the EMF and leukemia and brain cancer research studies, is not as informative for EMF and breast cancer research because breast cancer is rare in men, women are rare in electrical occupations, and because investigators cannot control for other known or suspected breast cancer risks. Studies that specifically look at populations with larger numbers of females in jobs with high EMF exposure, shift work, or exposure to light-at-night may be more useful. In addition, careful exposure definitions that include both residential and occupational EMF exposure as well as time period of exposure are needed. Careful control for known breast cancer risks, as well as evaluation of menopause and estrogen receptor status as effect modifiers, is needed to better understand the potential relationship between EMF and breast cancer.

Although most of the epidemiologic data do not provide strong support for an association between EMF and breast cancer, because of the limited statistical power as well as the possibility of misclassification and bias present in much of the existing data, it is not possible to rule out a relationship between EMF and breast cancer. Given the ubiquitous nature of EMF exposure and the high incidence of breast cancer, even a small risk will potentially have a substantial public health impact. Carefully designed studies that specifically test the hypothesis set forth by Stevens (*1*) are warranted.

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